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Fundamentals of Radiation Biology



Objectives

- **Describe chemistry of radiation absorption**
- **Describe cell survival curves and assay systems**
- **Describe interaction of ionizing radiation at cellular, tissue, and entire organism level**
- **Describe effect of dose rate**
- **Describe effect of time, dose, and fractionation**
- **Describe early and late reacting tissue response**
- **Describe acute effects of whole body radiation**
- **Describe oncogenic transformation 2° to radiation**



Radiochemical reactions

incident photon



fast electron

10^{-15} sec



ion radical

10^{-10} sec



free radical

10^{-5} sec



breakage of chemical bonds

$< 1 \text{ sec} \geq$



biological effects

hours to years



Direct & Indirect Action of Radiation

- Direct action:
 - Direct ionization of target
 - Secondary e^- directly ionizes target
- Indirect action:
 - Secondary e^- produces ion radicals that ionize target
 - Ion radicals produce free radicals that ionize target
- Indirect action predominates at $\approx 2:1$
- Water commonly ionized as cell is 80% water
- Evidence supports DNA as the critical target
- More recent evidence demonstrates “bystander effect”
 - Likely related to release of cytotoxic agents, presence of gap-junctions, and membrane damage

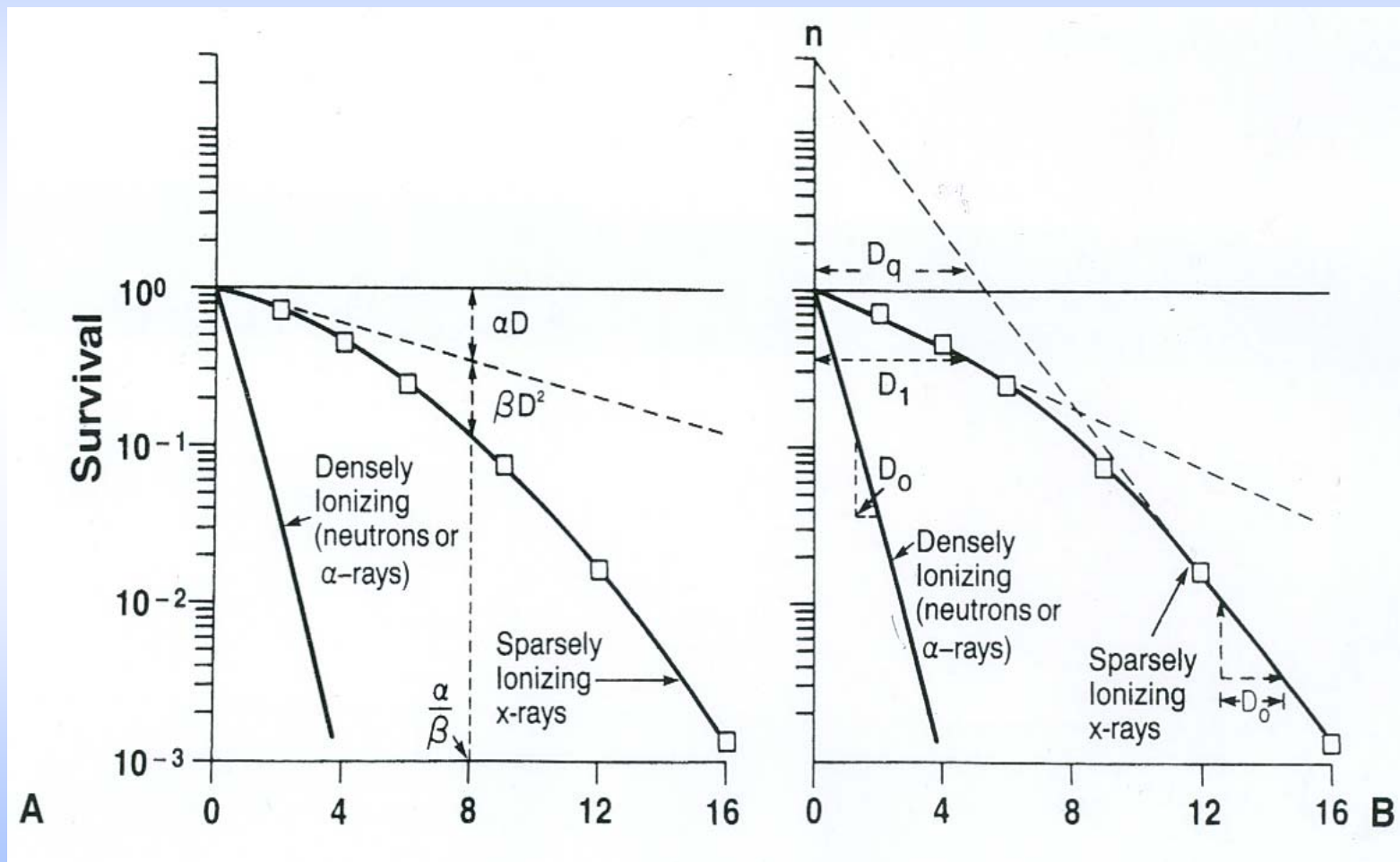


Radiolysis of Water (Saline)

- $\text{H}_2\text{O} \rightarrow \text{H}_2\text{O}^+ + \text{e}^-$ (solvated electron)
- $\text{H}_2\text{O}^+ + \text{H}_2\text{O} \rightarrow \text{H}_3\text{O}^+ + \text{OH}\cdot$ (hydroxyl radical)
- $2 \text{OH}\cdot \rightarrow \text{H}_2\text{O}_2$ (hydrogen peroxide)
- $\text{e}^- + \text{O}_2 \rightarrow \text{O}_2^-$ (dioxygen radical anion)
- $\text{OH}\cdot + \text{alkyl (R)} \rightarrow \text{ROH}\cdot$ (alkyl free radical)
- $\text{OH}\cdot + \text{Cl}^- \rightarrow \text{ClO}^-$ (hypochlorite anion)

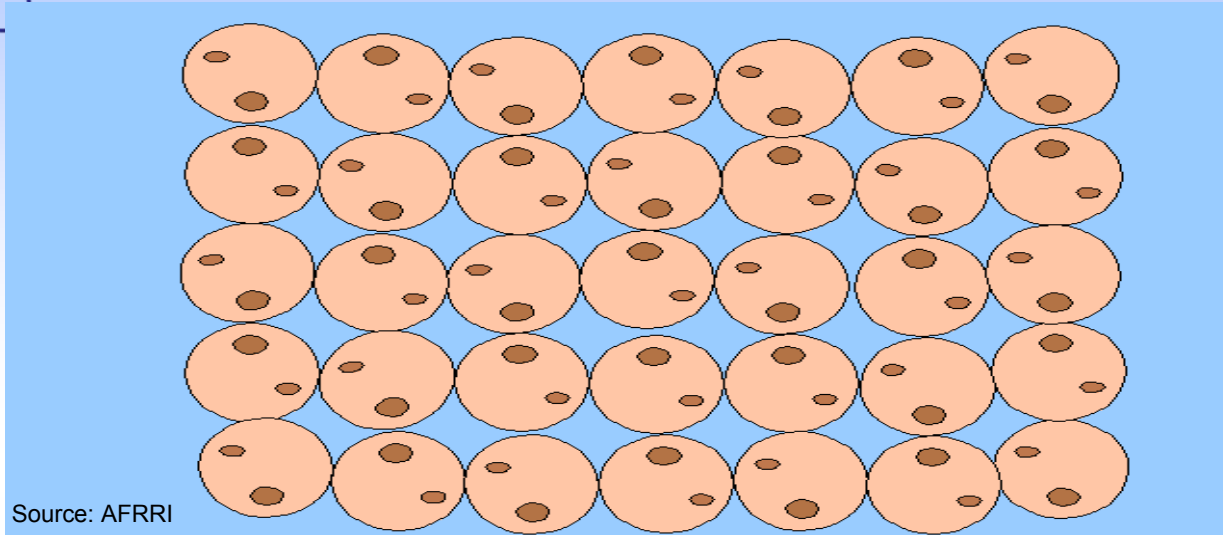


Cell Survival Curves





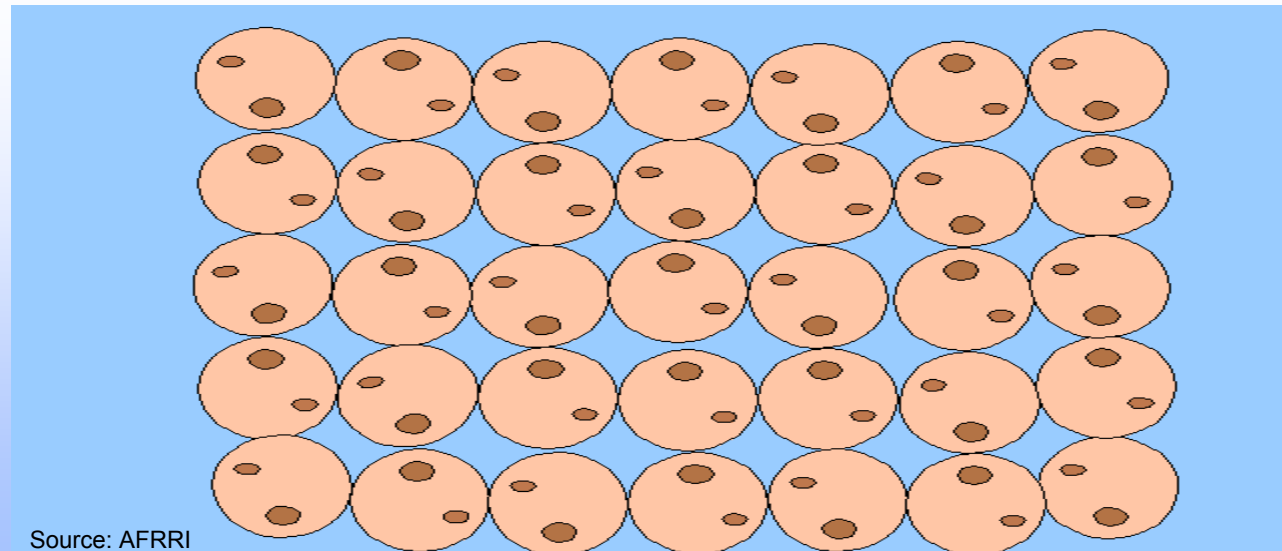
Linear Energy Transfer



Source: AFRRRI

Low LET
(photons)

High LET
(alpha particles)



Source: AFRRRI



Cell Survival Curves

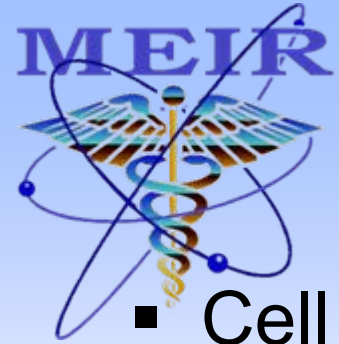
- Refer to article (p 260-261) for more complete review
- Surviving fraction per linear-quadratic model

$$S/S_0 = e^{-\alpha D - \beta D^2}$$

$$S/S_0 = e^{-\alpha/\beta D - D^2}$$

$$S/S_0 = e^{-(\alpha/\beta D + D^2)}$$

- Significance of the α/β ratio covered subsequently



Radiobiology Assay Systems

- Cell survival curves represent *in vitro* conditions
$$S/S_0 = \text{colonies counted}/(\text{cells seeded})(\text{PE}/100)$$
where PE is defined as the plating efficiency
$$\text{PE} = \text{cells seeded}/\text{cells that grow into colonies}$$
- Clonogenic end point assays determined by observing a clone of regenerating cells *in situ*
 - murine skin colony assay
 - murine jejunal crypt cell assay
 - murine testes stem cell assay
 - murine kidney tubule assay



Radiobiology Assay Systems

- Clonogenic assays from donor animals
 - eg: bone marrow stem cell assay
 - (sometimes called spleen colony assay)
 - step 1: lethally irradiate recipient mouse
 - step 2: radiate donor mouse to test dose
 - step 3: harvest bone marrow cells from donor mouse, form cell suspension, and inject into recipient mouse
 - step 4: harvest spleen from recipient mouse 10 days later and count colonies

$$S/S_0 = \text{colonies counted/cells inoculated} \times \text{PE}$$



Radiobiology Tumor System Assays

- Growth delay assay

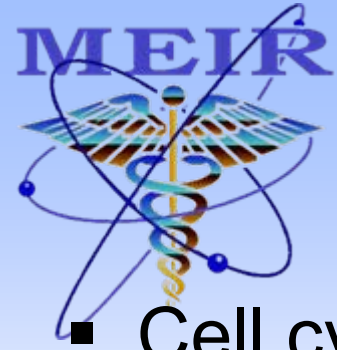
Radiate tumor and measure the time for regrowth to size at time of radiation or time to specified size

- TCD₅₀ assay (TDC = tumor control dose)

Radiate tumors of uniform size at graded doses in series of animals, measure proportion controlled, and score dose achieving 50% local control

- Lung colony assay

Radiate tumor to test dose, excise tumor, form cell suspension, inject into recipient mouse, harvest lungs 21 days later and count lung colonies



Radiosensitivity in the Mitotic Cycle

- Cell cycle: $G1 \rightarrow S \rightarrow G2 \rightarrow M \rightarrow G1$ etc.
Recall cells can enter in to and out of $G0$ from $G1$
- Time for M almost universally at 1 hour
- Time for $G2$ quite consistent at 3 to 4 hours
- Time for S usually 6 to 8 hours and not > 15 hours
- Time for $G1$ highly variable from 1 to > 12 hours
- Mitotic harvest technique
- Synchronized cells obtained by block at end of $G1$
Cells accumulate at block using hydroxyurea then progress through cell cycle when drug removed
- Refer to article (p 261) regarding cell survival curves



Classification of Radiation Damage

- Lethal damage

Occurs subsequent to cytocidal radiation dose

Damage irreversible and irreparable

Most cells die in association with mitosis*

Cell death usually occurs in subsequent mitosis

Cells that die mitotic death may require up to 5 mitoses

Some cells die from activated apoptotic pathways

Many cell populations die both mitotic and apoptotic

Radiosensitive cells tend to die from apoptosis

*Lymphocytes and oocytes die an interphase death



Classification of Radiation Damage

- Potentially lethal damage (PLD)
 - Cytocidal under normal growth conditions
 - Cell survival enhanced by modifying the post-irradiation cellular environment
 - Suboptimal growth conditions inhibit cell cycle progression and complex process of mitosis
 - Evidence indicates that PLD equates to DNA repair



Classification of Radiation Damage

- Sublethal damage (SLD)

Cell survival enhanced if total dose is divided in time

Two different patterns of repair demonstrated

Two fraction split dose experiments at 24°C & 37°C

One pattern of SLD repair demonstrated at 24°C

when cells do not progress through the cell cycle

More complex pattern of SLD repair shown at 37°C

→ Prompt repair of SLD seen in first few hours

→ Surviving fraction decreases reaching low at 5 hours

→ Surviving fraction then increases again



Four R's of Radiobiology

- Pattern of SLD repair based on mitotic cycle
 - Three simultaneous processes account for pattern
- Prompt repair of SLD occurs initially
- In asynchronous population most sensitive cells die
- Surviving population of becomes partly synchronized
- Radioresistant S-phase cells progress through cycle
- Cell cycle progression often termed reassortment
- Cell division of surviving fraction causes repopulation
- First three “R’s” = repair - reassortment - repopulation
- Fourth “R” = reoxygenation represents separate topic



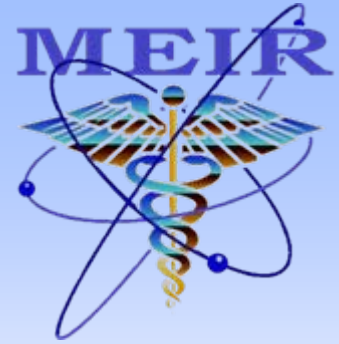
Dose Rate Effect

- Effect of dose rate extremely important
- Biologic effects strongly dependent on dose rate
- Dose rate effect essentially due to SLD repair
- Effect of dose rate separate from fractionation
- Refer to single page handout

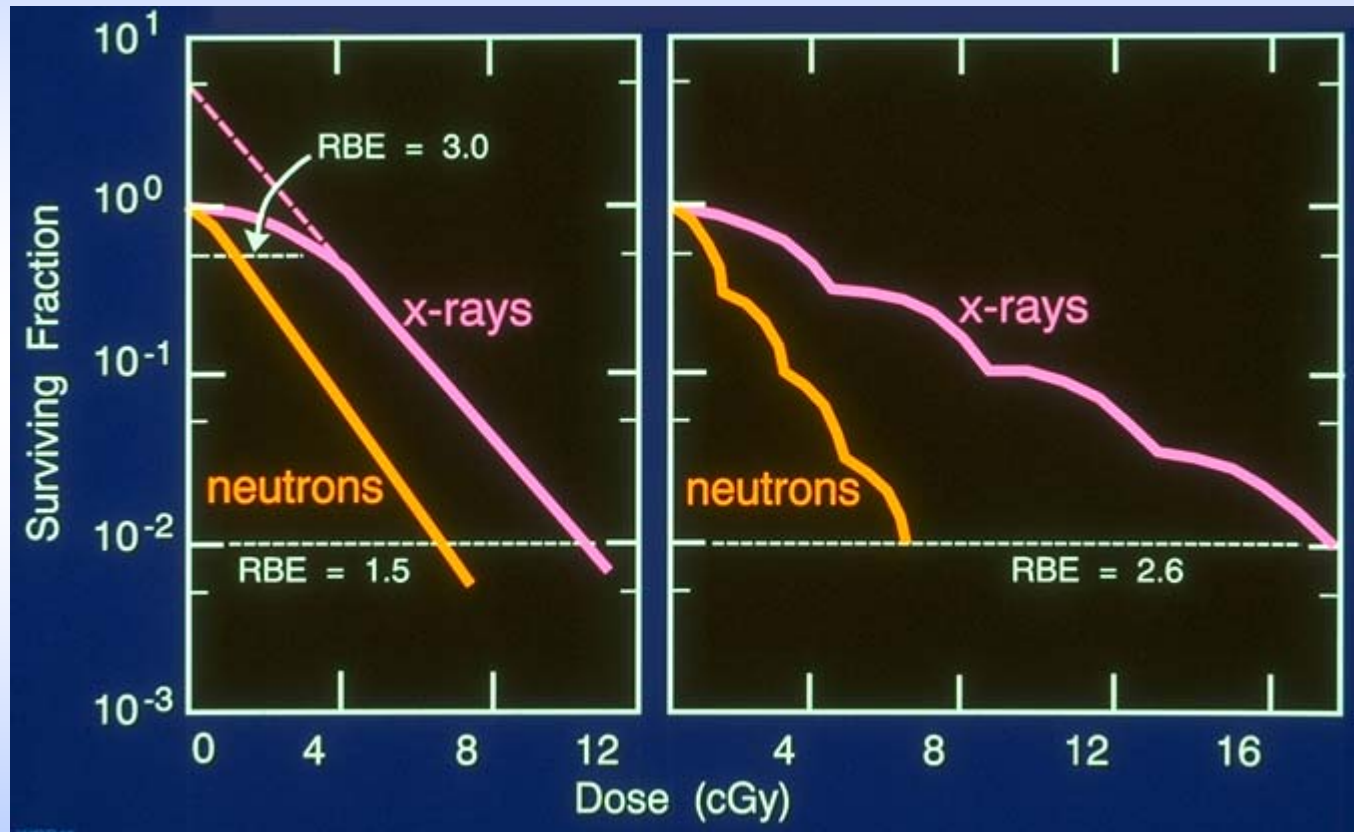


Time - Dose - Fractionation (TDF)

- Time, dose, & fractionation important in radiotherapy
- Time refers to the total time in days radiation delivered
- Dose refers to the total dose delivered
- Fractionation refers to the dose delivered per fraction
- Conventional fractionation = 1.8 to 2.0 Gy/day
- For a dose known to control a given burden of tumor at conventional fractionation, that dose must be increased when the standard treatment time exceeded
eg: 60 Gy over six weeks (thirty 2Gy/day fractions)
does not have the same biological endpoint as 60 Gy over ten weeks while 80 Gy over ten weeks might



Fractionated Cell Survival Curves





RBE and OER

- Relative biological effectiveness = $D_{250\text{kV}_P} / D_{\text{Test Radiation}}$
required for equivalent biological effect
- 250 kV_P x-rays “traditional” historic standard
- Numerical value of RBE dependent on isoeffect endpoint and can vary based on the TDF
- Oxygen enhancement ratio = $D_{\text{Hypoxic}} / D_{\text{Aerated}}$
required for equivalent biological effect
- Numerical value of OER dependent on isoeffect endpoint and can vary based on the TDF
- OER and reoxygenation only pertinent to radiotherapy



Early & Late Reacting Tissues

- At least two different tissue types recognized
- Early reacting tissues: actively mitotic
egs: skin & mucosa (buccal, intestinal, bladder)
- Late reacting tissues: post-mitotic
egs: connective tissue, bone, muscle, & nerve
- In linear-quadratic model, components of cell killing proportional to dose and $(\text{dose})^2$ are equal when $\alpha D = \beta D^2$ or $D = \alpha/\beta$
- The α/β ratio defines the type of tissue response
- Early reacting: $\alpha/\beta \approx 10$ Gy; late reacting: $\alpha/\beta \approx 2$ Gy
- Shape of cell survival curve differ (refer to figure)
- Volume of tissue irradiated extremely important



Acute Effects of Whole Body Radiation

- Exposure interval (time), dose, fractionation, and dose rate critically important determining clinical endpoint
- Effects of whole body radiation significantly different compared to partial body or localized radiation
- “Classic” acute radiation syndromes (ARS) based on single fraction whole body exposure at high dose rates
- Syndromes follow three phases referred to as the prodromal phase, latent phase, and manifest illness
- Duration of each phase and interval between phases varies depending primarily on total dose and dose rate
- Mixed photon/neutron beams may worsen prognosis



Acute Effects of Whole Body Radiation

- Traditional ARS includes cerebrovascular syndrome gastrointestinal syndrome & hematopoietic syndrome
- Recent approaches to the classification of ARS have shifted to five tiers of predicted clinical severity

Mild	Moderate	Severe	Very Severe	Lethal
1-2 Gy	2-4 Gy	4-6 Gy	6-8 Gy	> 8 Gy
- Predicted onset of symptoms, clinical manifestations, and laboratory findings developed for each category
- Overall prognosis and treatment recommendations provided for each of the five classifications
- Refer to single page handout



Radiation Induced Oncogenic Transformation

- Radiation capable of producing genetic changes
- Genetic alterations shown to be the cause of cancer
- Cancer development to two contributing processes
- Conversion of proto-oncogenes to oncogenes represents the gain of oncogenic potential
- Loss of tumor suppressor genes (emerogenes) represents the loss of anti-oncogenic potential
- Emergence of radiation induced oncogenic phenotype secondary to “balance” of transformation & cell killing
- Refer to single page handout



Thank you for your attention

- Questions
- Comments
- Discussion

